Postoperative improvement of brain maturation in infants with congenital heart disease

Hottinger, Selma J ; Liamlahi, Rabia ; Feldmann, Maria ; Knirsch, Walter ; Latal, Beatrice ; Hagmann, Cornelia F

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Postoperative Improvement of Brain Maturation in Infants With Congenital Heart Disease

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Children with severe congenital heart disease are at risk for neurodevelopmental impairments. We examined brain maturation in infants undergoing neonatal cardiopulmonary bypass surgery or hybrid procedure for hypoplastic left heart syndrome compared to controls. This is a prospective cohort study on term-born infants with congenital heart disease with cerebral MRI pre- and postoperatively. Healthy infants served as controls. Brain maturation was measured using a semiquantitative scoring system. The progress of brain maturation from the preoperative to postoperative MRI within patients was compared. Neurodevelopment was assessed at 1 year with the Bayley Scales of Infant and Toddler Development III. A total of 92 patients with congenital heart disease and 46 controls were studied. Median total maturation score in patients was 12 (interquartile range 10.6–13.0) preoperatively and 14 (12.0–15.0) postoperatively, in controls it was 14 (13.0–15.0). Median time interval between scans was 19 days (interquartile range 14–26). After correction for postmenstrual age at MRI, the pre- and postoperative maturation score was lower in patients compared to controls (preoperative $P = 0.01$, postoperative $P = 0.03$) and increased between pre- and postoperative assessment ($P \leq 0.001$). Brain maturation scores did not correlate with neurodevelopmental outcome at 1 year, when corrected for socioeconomic status and postmenstrual age at MRI. This study confirms delayed brain maturation in children with congenital heart disease, and despite neonatal cardiac bypass surgery followed by postoperative intensive care medicine brain maturation is ongoing. We encourage further investigation in outcome prediction in this population, potentially by combining more advanced MRI measures with clinical methods.

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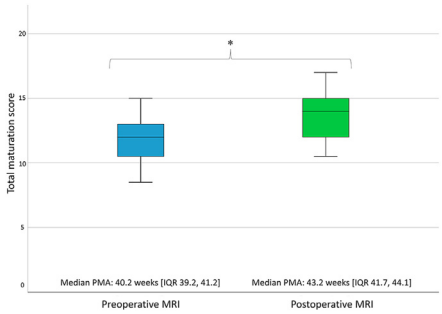

Perioperative improvement in brain maturation in infants with congenital heart disease.

Central Message

Brain maturation in infants with congenital heart disease is delayed compared to healthy controls and shows an ongoing maturation after cardiac surgery.

Perspective Statement

Infants with congenital heart disease show delayed brain maturation which potentially contributes to higher cerebral vulnerability and later neurodevelopmental impairments. Combining more advanced MRI measures with clinical, structural, and functional methods will help to improve outcome prediction.

Abbreviations: AUC, area under the curve; CHD, congenital heart disease; d-TGA, d-transposition of the great arteries; GA, gestational age; HC, head circumference at birth; IQR, interquartile range; ROC, receiver operating characteristic; Sd, standard deviation; SES, socioeconomic status; TMS, total maturation score; WMI, white matter injury

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Keywords: Congenital heart disease, Brain maturation, Neurodevelopmental outcome

INTRODUCTION

Impaired neurodevelopmental outcome is the most significant extracardiac morbidity of infants with congenital heart disease (CHD), however, the underlying mechanisms are to date not fully understood.[1,2] Over the last decades, cardiac mortality and morbidity of patients with CHD have significantly improved,[3] whereas only little improvement of their neurodevelopment has occurred.[2] There is evidence that brain maturation is delayed in CHD infants.[4-6] This might potentially be due to altered fetal hemodynamics and cerebral perfusion[7,8] and could have an impact on neurodevelopment. A semiquantitative total maturation score (TMS) has been developed by Childs et al and combines elements of myelination, cortical infolding, germinal matrix distribution, and glial cell migration.[9] This score has been validated in preterm infants without brain injury and term infants up to 41 weeks' gestational age (scanned at 24−43 weeks of postmenstrual age [PMA]). It is significantly related to PMA and increases with progressive brain maturation.[9] TMS could be a useful tool for investigation of brain maturation in CHD infants that is relatively easy to apply. Licht et al demonstrated in a group of 42 neonates with CHD that the preoperative TMS was lower than in the normative data suggesting a delay of approximately 1 month in structural brain development.[5] The progression of TMS after surgery has not been examined yet and only 1 study reported the association between TMS at 3 months of age and neurodevelopmental outcome.[10]

We therefore aimed to determine pre- and postoperative brain maturation using the TMS in a currently enrolled cohort of neonates with CHD in comparison to healthy control infants. We hypothesized that brain maturation in infants with CHD would be delayed preoperatively, improve postoperatively, and would be associated with early neurodevelopmental outcome at 1 year of age. We also examined the impact of CHD severity on the perioperative trajectory of brain maturation.

METHODS

Patients

In this prospective cohort study, neonates with CHD born >36 weeks of gestation were enrolled at the University Children's Hospital Zurich between December 2009 and July 2018. Inclusion criteria were planned neonatal cardiopulmonary bypass surgery or hybrid procedure for hypoplastic left heart syndrome within the first 3 months of life. Patients with suspected or proven genetic syndromes and neonates born <36 weeks of gestation were excluded, as these factors are known to be independent risk factors for impaired neurodevelopmental outcome. Healthy term-born control infants were recruited between January 2011 and November 2017 at the maternity unit of the University Hospital Zurich. Written parental informed consent was obtained. Demographic and medical variables of all infants were prospectively collected. Parental socioeconomic status (SES) was estimated by means of maternal education and paternal occupation (total score range 2−12, with higher scores indicating higher SES).[11] The Ethical Committee of the Canton of Zurich approved the study (KEK StV-23/04 and StV-19/04).

Cerebral MRI

MRIs were performed on a 3-Tesla MRI scanner (SignaHDxt, GE Healthcare, Milwaukee, WI) using an 8-channel head coil (GE Signa MR750). The scanning protocol included axial T1-weighted spin-echo sequence (repetition time TR = 680 ms; echo time TE = 21 ms) with a slice thickness of 2.5 mm, and T2-weighted fast-spin-echo sequences in 3 planes with a slice thickness of 2.5mm (TR = 5300 ms; TE = 102 ms).

Brain Development

Brain development was assessed using the TMS developed by Childs et al.[9] The TMS consists of 4 subscores: Germinal matrix distribution was assessed on the whole brain on T2-weighted axial images, whereas cortical infolding and glial cell migration were assessed on the T1 and T2-weighted axial images closest to the foramen of Monro. Myelination was scored separately on T1- and T2-weighted images, whereas the average was considered as myelination score.[9] The MRIs were scored by 1 observer (C.H.) who was blinded to group, diagnosis, clinical course, and neurodevelopmental outcome. For investigation of the interrater reliability 2 raters (C.H. and R.L.) independently scored 10 MRIs. Cronbach's alpha was 0.74 ($P < 0.01$).

Brain Injuries

White matter injury (WMIs) was defined as focal area of abnormal T1 hyperintensity. Arterial ischemic stroke was defined as a homogeneous area of altered signal intensity on T1 and T2-weighted images with a specific arterial distribution involving cortical grey matter and/or basal ganglia and/or thalamus.

Neurodevelopmental Outcome

Neurodevelopmental follow up assessment at 1 year was performed at the Child Development Center at the University Children's Hospital Zurich using the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley III).[12] The Bayley III provides 3 composite scores: the cognitive, language, and motor composite score, with a mean test score of 100 and standard deviation (sd) of ±15.

Statistical Methods

All statistical analyses were performed using IBM SPSS statistics software version 25.0 (IBM, Armonk, NY). Descriptive statistics were used to characterize the demographic and clinical characteristics of the study population. Values are expressed as mean and sd or median and interquartile range (IQR) for variables not normally distributed. Comparison between groups for continuous variables was performed using *t*-tests and Mann-Whitney *U* tests depending on the sample distribution. Comparisons for categorical variables were assessed by Fisher's exact test. Pre- and postoperative TMS were compared using Wilcoxon signed-rank test for dependent samples in patients who underwent serial imaging. Effect size was calculated as $r = |z/\sqrt{n}|$ and r > 0.40 was considered a large effect size. All statistical tests were 2-sided and *P* values ≤0.05 were considered statistically significant.

To explore the ability of the TMS and its respective subscores to classify CHD infants and control infants, a receiver operating characteristic curve of the preoperative scores was plotted, and the area under the curve (AUC) calculated. Explorative correlation analyses were performed using bivariate nonparametric Spearman correlation to assess correlations between TMS and outcome as well as head circumference at birth (HC) and outcome. These analyses were performed for the entire cohort of CHD and control infants, to increase the power of the analysis.

As TMS is significantly related to PMA at scanning, we used multiple linear regression models to correct for PMA. The same model was used to correct neurodevelopmental outcome for SES. There was no difference in sex in the age-corrected TMS. Therefore, sex was not considered as a confounder in the further analysis. Thus, multiple linear regression models, corrected for PMA and SES, were calculated to assess the association of TMS with neurodevelopmental outcome in CHD infants. Furthermore, explorative multiple linear regression models, corrected for SES, were calculated to assess the association of HC and outcome in CHD infants.

RESULTS

Study Population

A total of 92 patients with CHD and 46 control infants were included. The majority of infants had a d-transposition of the great arteries (n = 43, 46.7%) and 21 infants (22.8%) had univentricular diagnoses (for a detailed list of CHD diagnoses see Table 2). Compared to controls, CHD infants were more likely to be male, had lower median HC at birth and a lower median parental SES than control infants (Table 1).

Of the 92 enrolled patients, 70 (76.1%) underwent preoperative cerebral MRI (median age 7 days, IQR 5−9 days), whereas the remaining patients were clinically not stable enough to be transferred to the MR-Scanner preoperatively. A total of 85 patients (92.4%) underwent postoperative cerebral MRI as soon as they were clinically stable (median age 25 days, IQR 20−32 days). Reasons for missing postoperative cerebral MRI were the inability to perform the MRI in natural sleep (n = 4) or logistic reasons (n = 2); 1 child died postoperatively. The quality of 1 postoperative MRI was not sufficient for analysis. Serial images were thus available in 62 patients. All control infants had a single cerebral MRI at a median age of 21 days (IQR 16−28 days). Median PMA at preoperative cerebral MRI was lower in CHD patients than in control infants, while

Table 1. Characteristics of Infants With Congenital Heart Disease and Control Infants

	CHD	Controls	*P* Value
n	92	46	
Birth weight, g (m [sd])	3323.5 (468.2)	3420.5 (415.0)	0.244
Male sex, n (%)	65 (70.7)	21 (45.7)	0.008
GA, wks (m [sd])	39.4 (1.3)	39.5 (1.2)	0.496
Head circumference at birth, cm (m [sd])	34.5 (1.3)	35.1 (1.2)	0.033
Apgar at 5′ (M [IQR])	9.0 [8.0, 9.0]	9.0 [9.0, 9.0]	0.256
SES (M [IQR])	9.0 [7.0, 10.0]	12.0 [10.0, 12.0]	<0.001
PMA at the preoperative MRI, wks (M [IQR])	40.2 [39.3, 41.4]	42.3 [41.1, 44.1]	<0.001
PMA at the postoperative MRI, wks (M [IQR])	43.3 [41.8, 44.1]	42.3 [41.0, 44.1]	0.173
Preoperative TMS (M [IQR])	12.0 [10.6, 13.0]	14.0 [13.0, 15.0]*	<0.001
Postoperative TMS (M [IQR])	14.0 [12.0, 15.0]	14.0 [13.0, 15.0]*	0.45
Age at Surgery, d (M [IQR])	11.0 [8.0, 15.0]		
Preoperative intubation, n (%)	47 (51.1)		
Postoperative ECMO, n (%)	3 (3.5)		
Postoperative seizures, n (%)	3 (3.3)		
Length of first hospital stay,d, (M [IQR])	30.5 [25.0, 42.8]		
Length of first intensive care stay,d, (M [IQR])	9.0 [6.0, 14.8]		

CHD, congenital heart disease; GA, gestational age; IQR, interquartile range; M, median; m, mean; PMA, postmenstrual age; sd, standard deviation; SES, socioeconomic status; TMS, total maturation score.

Groupwise comparison for categorical variables was performed by Fisher's exact test and for continuous variables *t*-test and Mann-Whitney *U* test were applied appropriate for sample distribution.

*As only one MRI was performed in controls, the pre- and postoperative TMS in this table are the same data in controls.

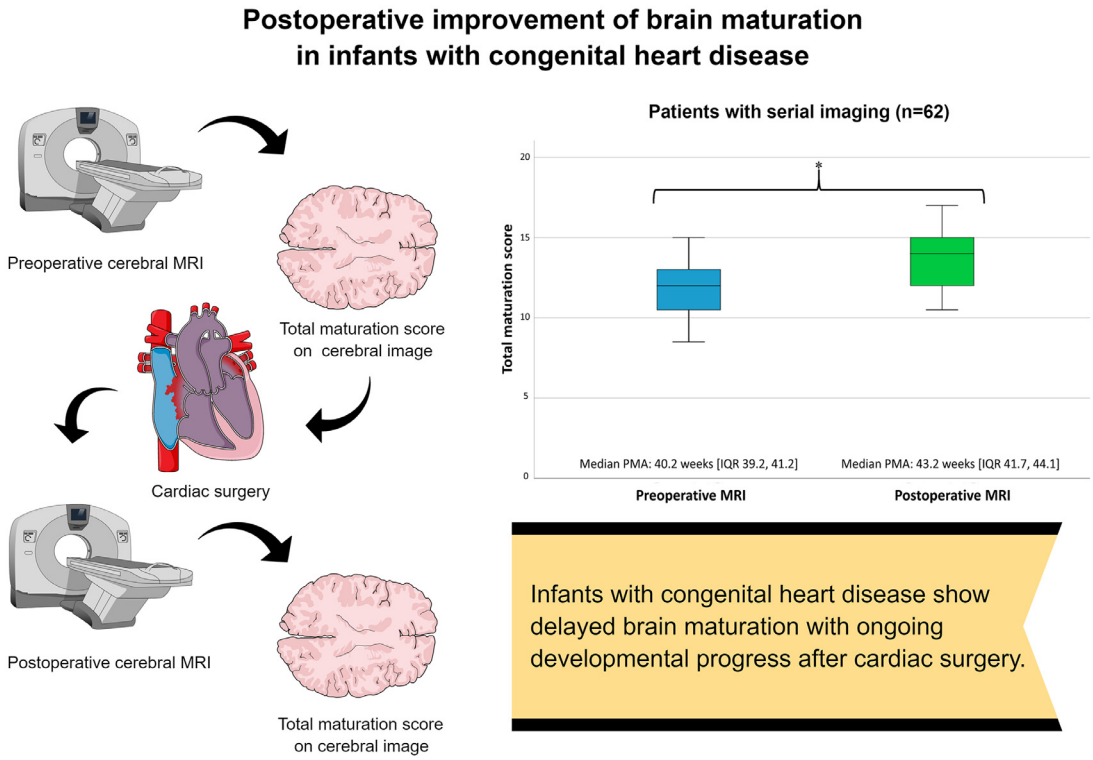

Figure 1. Graphical abstract.
Key points of the study including methods (left), main results (top right) and conclusion (bottom right). Infants with congenital heart disease underwent cerebral MRI prior and after cardiac surgery. By means of a standard score, brain maturation on each cerebral image was determined. Longitudinal data was then analyzed in patients with serial imaging, showing an ongoing maturation after cardiac surgery.

median PMA at postoperative cerebral MRI was similar to PMA at scan in controls infants (Table 1). MRI was performed in natural sleep in all controls. Some CHD infants had a clinical indication for sedation (2 preoperatively, 5 postoperatively) or intubation (8 preoperatively, 1 postoperatively).

Total Maturation Score

Preoperative median TMS was lower in CHD infants than in controls while postoperative TMS was similar (Table 1). After correction for PMA in the multiple linear regression, the pre- and postoperative TMS was lower in CHD patients than in control infants (preoperative MRI $P = 0.01$, postoperative MRI $P = 0.03$). As illustrated in Figure 2, receiver operating characteristic analysis of the TMS and its subscores showed the largest AUC for the full TMS (AUC results: TMS = 0.82 [95%CI 0.74−0.89], myelination = 0.66 [95%CI 0.56−0.76], cortical folding = 0.77 [95%CI 0.68−0.87], germinal matrix = 0.65 [95%CI 0.55−0.75], bands of migrating cells = 0.745 [95%CI 0.65−0.83]). The optimal cut-off for TMS is 12.5 corresponding to a specificity of 84% and a sensitivity of 80%.

Trajectories of Brain Maturation

Of all patients, pre- and postoperative MRI were performed and scored in 62 patients. Analysis of this subset of patients compared to controls revealed that the group difference in brain maturation was significant preoperatively but not postoperatively (controlling for PMA in linear regression: preoperative MRI $P = 0.03$, postoperative MRI $P = 0.145$).

The median TMS increased from pre- to postoperative assessment (Wilcoxon signed-rank test: $r = 0.815$, $P \leq 0.001$) (Fig. 3). Trajectories of brain maturation of patients with serial imaging was visualised in Figure 4. Wilcoxon signed-rank test was also performed for the different diagnostic groups, whereas both, univentricular and biventricular diagnoses, showed a significant change in TMS from pre- to postoperative MRI with a large effect size (univentricular diagnoses: $r = 0.842$, $P = 0.011$, biventricular diagnoses: $r = 0.812$, $P \leq 0.001$).

Severity of CHD and TMS

We did not find a significant difference in age-corrected TMS between uni- and biventricular CHD ($P = 0.892$ preoperatively, $P = 0.718$ postoperatively), nor between dominant right or left systemic ventricle in univentricular CHD ($P = 0.648$ preoperatively, $P = 0.994$ postoperatively). However, the number of infants with univentricular type of CHD was small (Table 2). Likewise, there was no significant difference in age-corrected TMS between cyanotic and noncyanotic CHD infants ($P = 0.921$ preoperatively, $P = 0.435$ postoperatively).

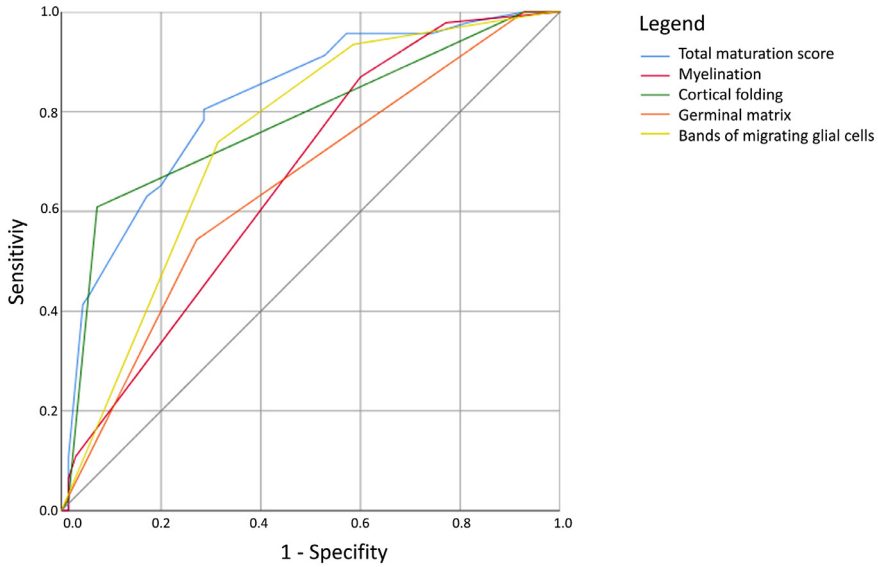

Figure 2. Receiver operating characteristic (ROC) curve of the total maturation score and its composing subscores in the preoperative cerebral MRI of infants with congenital heart disease and controls.
ROC curves show the ability of the total maturation score and its subscores to differentiate patients with congenital heart disease from healthy controls. Higher area under the curve (AUC) indicate a better discriminative ability. The total maturation score (AUC = 0.820) consists of the following subscores: myelination (AUC = 0.665), cortical folding (AUC = 0.779), germinal matrix (AUC = 0.652) and bands of migrating cells (AUC = 0.745). Therefore, the full score suits best to classify into study groups and should not be abbreviated.

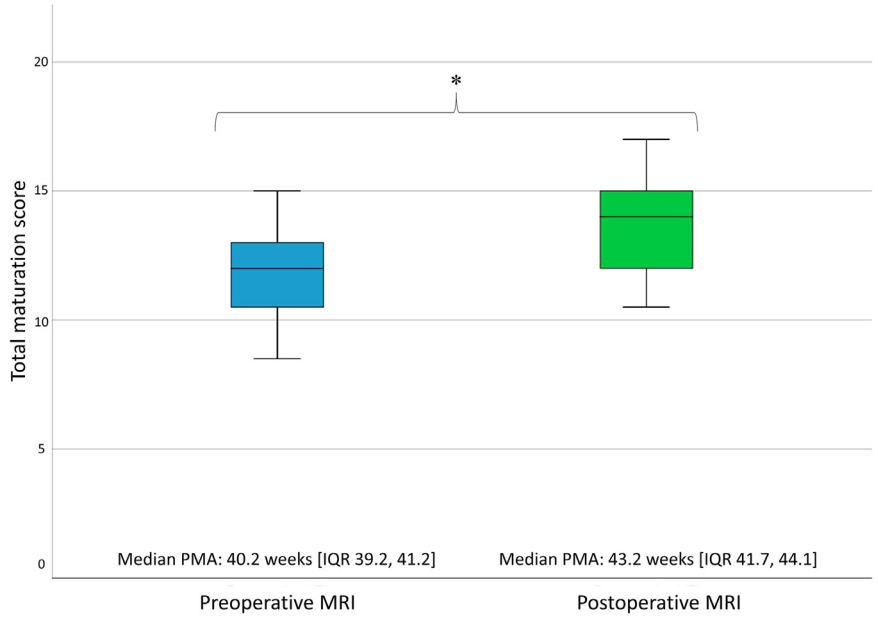

Figure 3. Perioperative improvement in brain maturation in infants with congenital heart disease.
Box-and-whiskers plot depicting the median (horizontal bar) and interquartile range (box) of total maturation score in serial cerebral MRI of infants with congenital heart disease preoperatively (blue) and postoperatively (green). Median and interquartile range (IQR) of postmenstrual age (PMA) at time of scanning is declared.
* Wilcoxon signed-rank test shows a significant improvement of brain maturation with a large effect size ($r = 0.815$, $P \leq 0.001$). (Color version of Figure is available online.)

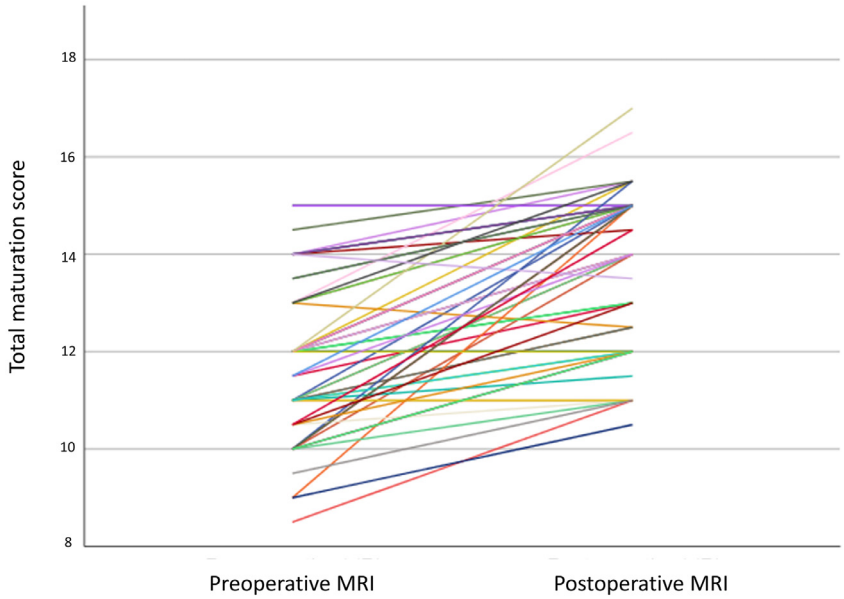

Figure 4. Trajectories of brain maturation in patients with congenital heart disease from preoperative to postoperative MRI. The x-axis represents the time points of imaging, y-axis shows total maturation score reflecting brain maturation at time of imaging. The progression of brain maturation of each patient who underwent imaging prior and after cardiac surgery, is represented by a separately colored line.

Table 2. Cardiac Diagnoses of the CHD Patients

Cardiac Diagnosis, n (%)	Total n = 92
d-Transposition of the great arteries (dTGA)	43 (46.7)
Univentricular heart (single right)	15 (16.3)
Univentricular heart (single left)	6 (6.5)
Interrupted aortic arch or severe aortic arch hypoplasia/coarctation	8 (8.7)
Double outlet right ventricle*	9 (9.8)
Total anomalous pulmonary venous return	2 (2.2)
Ventricular septal defect	1 (1.1)
Atrioventricular septal defect	1 (1.1)
Tetralogy of Fallot	1 (1.1)
L-transposition of the great arteries	1 (1.1)
Pulmonary atresia with ventricular septal defect	1 (1.1)
Pulmonary atresia	1 (1.1)
Truncus arteriosus communis	1 (1.1)
Critical aortic valve stenosis	1 (1.1)
Borderline left ventricle with a bicuspid aortic valve	1 (1.1)

*DORV population were associated with D-TGA type (n = 7)

For all patients who underwent serial imaging, we also investigated the progression of the TMS between the preoperative and postoperative MRI corrected for days between scans. We could not find a significant difference in the progression between diagnostic groups (P = 0.550 for right vs left systemic ventricle, P = 0.417 for univentricular vs biventricular, P = 0.444 for cyanotic vs acyanotic CHD).

Brain Injuries

In 14 of 70 patients preoperatively (20%) and 17 of 85 patients postoperatively (20%) any brain injuries on cerebral MRI were detected (WMI and/or stroke). None of the control infants had a brain injury. The presence of brain injury was not associated with age-corrected preoperative TMS (P = 0.35), nor with postoperative TMS (P = 1.09) using multiple linear regression analysis.

Neurodevelopmental Outcome at 1 Year

Neurodevelopmental follow up at 1 year (median age 13 months, IQR 12−13 months) was performed in 85 of 92 included patients and in 40 of 46 controls. Of the remaining 13 children, 2 CHD patients had died, and 5 patients and 6 controls were lost to follow up. Reasons for loss of follow-up were parents not wanting to participate (n = 8) or families who moved abroad (n = 3). Thus, the follow-up rate for CHD patients was 94.4% and for controls 87.0%.

The mean cognitive and motor composite scores of the Bayley III were lower in children with CHD compared to controls (cognitive composite score: 105.6 [sd 14.7] vs 116.9 [sd 11.0]; $P \leq 0.001$, motor composite score: 91.6 [sd 14.1] vs 103.3 [sd 10.9]; $P \leq 0.001$). The mean language composite score was lower but not statistically different between CHD and controls (93.9 [sd 12.4] vs 97.9 [sd 10.0], P = 0.076). SES correlated with each domain of the Bayley III (cognitive composite score: r = 0.402, $P < 0.001$, motor composite score: r = 0.236, $P < 0.001$, language composite score: r = 0.245, P = 0.008). After correction for SES, cognitive and motor composite scores remained lower in children with CHD compared to controls (cognitive composite score P = 0.018, motor composite scores P = 0.004). HC at birth correlated with the cognitive composite score at 1 year (r = 0.225, P = 0.016). After correcting for SES,

the association remained significant (cognitive composite score: $P = 0.004$, motor composite score: $P = 0.037$).

Association of TMS With Neurodevelopmental Outcome

Explorative correlation analysis for the whole group showed an association between the preoperative TMS and the cognitive ($r = 0.307$, $P = 0.002$) as well as the motor score ($r = 0.245$, $P = 0.012$) at 1 year, while the postoperative TMS did not correlate with outcome. When examining CHD and controls separately, the correlations did not remain significant.

After correcting for SES and PMA, the association between preoperative TMS and outcome did not remain significant (motor composite score: $P = 0.43$, cognitive composite score: $P = 0.39$, language composite score: $P = 0.94$). Regarding the subscores of TMS, none of them were associated with outcome at 1 year when corrected for SES and PMA.

DISCUSSION

In this prospective cohort study, we demonstrated that infants with CHD show delayed brain maturation on pre- and postoperative MRI. As there was an increase in TMS between pre- and postoperative scan, we can show that the brain continues to mature in CHD even shortly after major heart surgery. We could, however, not find an association between brain maturation assessed by TMS and early neurodevelopmental outcome after controlling for SES and PMA at scanning. Also, infants with specific CHD diagnoses did not have a higher risk for maturational delay. Investigating the subscores of the TMS revealed that the full score discriminated best between CHD and controls and no specific subscore was particularly delayed. Therefore, we suggest using the TMS for describing maturation in this population.

To our best knowledge, we are the first to analyse TMS and its progression from the preoperative to the postoperative scan in CHD infants. For these analyses only patients who underwent serial imaging were included. However, excluding patients with only postoperative imaging may have led to a sample of less severely affected infants. As one of the reasons for missing preoperative MRI was clinical instability due to the severity of their heart defect, these patients may have potentially had lower TMS scores than stable patients. As control infants underwent only 1 scan, no longitudinal data for comparison of the slope of TMS progression between infants with CHD and controls were available.

Regarding the analyses within subsets of CHD infants, we expected a more distinct delay in univentricular type of CHD and especially in those with right systemic ventricle univentricular CHD, however we could not confirm this hypothesis. This might implicate that the presence of a CHD itself has more impact on brain maturation than the type of CHD. This is supported by fetal cerebral MRI studies showing a similar effect on brain growth delay for fetuses with hypoplastic left heart syndrome and transposition of the great arteries.[7,13] The lack of significant difference of TMS progression from the pre- to the postoperative MRI between diagnostic groups suggests that the progress of maturation itself is similar for all CHD infants but still delayed compared to healthy infants even on postoperative imaging. However, it could also be due to the small sample sizes in the subgroup analyses. Furthermore, this might also be attributable to the rather gross visual rating of structural brain maturation by the TMS, which might not capture the whole fingerprint of more subtle and complex maturational differences in microstructure, volume, and structural and functional connectivity.

The degree of delay in brain maturation in our study (median preoperative TMS 12) was less pronounced than that reported in 2 previous studies using the same scoring system.[5,10] Licht et al reported the mean TMS to be 10.15 in a cohort of 42 infants with both hypoplastic left heart syndrome and d-transposition of the great arteries born at a mean gestational age of 38.9 weeks and scanned at a mean age of 4.1 days.[5] Beca et al reported the mean preoperative TMS to be 10.3 for infants without WMI and 9.8 for infants with WMI in a cohort of 153 infants undergoing open-heart surgery, born at a mean gestational age of 38.8 weeks and scanned before surgery at a mean age of 7 days as well as 7 days after surgery and at the age of 3 months.[10] In our cohort, both pre-and postoperative age at MRI was rather old. The validation of the scoring system has only been performed until 43 weeks of gestation. But the original score covers myelination beyond this age and it therefore seems appropriate to use this tool beyond 43 weeks of gestation.[10] The range of severity of cardiac diagnoses in our cohort was smaller than in other studies. Whereas in Beca's cohort 19% of the CHD group were single ventricle hearts and another 28% were single ventricle with aortic arch obstruction, in our cohort only 23% had univentricular diagnoses.[10] The different composition of diagnoses could have led to less variation in TMS and higher chances to catch up with the healthy infants.

Beca et al analysed the association of brain maturation using this TMS with neurodevelopment at 2 years of age in a cohort of 153 CHD patients but no control infants.[10] Interestingly, brain maturation only on the 3 month MRI correlated with neurodevelopmental outcome in all 3 measured domains at 2 years of age. However, on the preoperative MRI, only delayed maturation of the posterior limb of the internal capsule was related to a lower motor score.[10] Two facts might explain the lack of association with outcome in our cohort: first, in our model, we adjusted for SES, whereas Beca et al did not incorporate SES into their multivariate regression. Second, we have assessed the children at 1 year of age, and outcome assessment might not reflect the extent of later neurodevelopmental impairment.

While other studies[10,14,15] have demonstrated that lower brain maturation scores, hence more immaturity, is a risk factor for WMI, we were unable to confirm this association in our population. Preoperative injury (WMI and/or stroke) (15.2%) in our study had a prevalence similar to other studies, which report ranges from 16 to 21 percent for preoperative

WMI.[5,10,14,15] A possible explanation for this difference may as well be the different composition of the cohorts with respect to cardiac diagnoses.

A study by Lim et al showed an association between cerebral oxygen delivery and TMS suggesting a link between fetal brain development and neonatal hemodynamics.[8] Although no causal relationship was established, their result supports the possibility of an impact of the hemodynamics in infants with CHD on brain development.

Another recent study by Lim et al investigated perioperative brain growth and neurodevelopment at 18 months in a cohort of 45 infants with transposition of the great arteries undergoing surgical repair.[16] They found a decrease in brain weight z scores perioperatively in 35 of 45 patients. Their analyses are based on brain volumes converted to estimated brain weight whereas this study focuses on the maturational progress of the brain. In our study, birth HC was smaller in CHD infants compared to controls and correlated with motor and cognitive outcome at 1 year. This is in line with previous publications showing a relatively strong association of HC at birth with early and also late neurodevelopmental outcome.[17-21] This indicates that HC at birth may be used as a clinical prognostic tool in infants with CHD.

It is a strength of the study that we report the comparison to term-born control infants. However, a limitation of this study is the small size of the control group compared to the CHD group as well as the size of the subgroups within patients. An additional limitation is the variation of PMA at time point of scanning, which was thus corrected for in multiple regression analyses. Regarding the neurodevelopmental outcome, the higher SES of the control infants' parents might have led to a bias towards better neurodevelopmental outcome in the control group. In addition, outcome assessment at 1 year of age is only a proxy of later developmental outcome, and correlation between early assessment and later school performance is poor.[22] As more specific examination of neurodevelopment is feasible at higher age, we hypothesise that the delay in brain maturation after birth might correlate better with cognitive functions at school age. Thus, school age follow-up needs to be performed in this at risk population.

In conclusion, we were able to demonstrate the effect of CHD on brain maturation in a sample of infants with a wide range of CHD diagnoses who underwent CPB surgery within the first 3 months of life and show the progression of brain maturation from pre- to postoperative imaging. Additional tools to describe brain maturation of infants at a higher PMA but just as easy to learn for clinical use as the TMS are needed for further investigations. In future studies, we will also use high-density EEG to assess brain maturation and quantify possible delay in brain maturation to improve the understanding of brain maturation in this population and in order to improve outcome prediction.

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The graphical abstract (Fig. 1) was created in the Mind the Graph platform, available at www.mindthegraph.com.

SUPPLEMENTARY MATERIAL

The following is the supplementary data to this article:

Video 1. This video explains the aims, methods and results of this study.

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